UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/028,395	02/24/98	PROCKOP	D 9598-32

HM22/1004

KATHRYN DOYLE LEARY
PANITCH SCHWARZE JACOBS & NADEL
ONE COMMERCE SQUARE
2005 MARKET SQUARE 22ND FLOOR
PHILADELPHIA PA 19103-7086

EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	6

DATE MAILED: 10/04/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/028,395	Prockop et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Feb 24, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, *Substitute* PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, *Substitute* PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Information Disclosure Statement, filed on 2/24/98, has been entered.

Claims 1-20 are being examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of treating a human patient having a disease, disorder or condition of the central nervous system (CNS) comprising obtaining a bone marrow sample from a human donor, isolating stromal cells from the bone marrow and administering the isolated stromal cells to the CNS of the human patient. The disease, disorder, or condition can be a genetic defect disease, a tumor, i.e., a brain tumor, trauma, stroke, or injury to the tissues or cells of the CNS. The cells can be transfected with an isolated nucleic acid encoding a therapeutic protein, which can be a cytokine, a chemokine or a neurotrophin. The nucleic acid can be a wild type copy of a mutated, non-functioning or under-expressed gene. The isolated stromal cells can be immunologically isolated.

The specification broadly discloses different diseases, conditions, and disorders which can be treated by cell therapy, and broadly discloses *ex vivo* gene therapy strategies for treating the diseases, conditions, or disorders of the CNS. However, the specification is non-enabling for the

claimed methods as the specification does not provide sufficient guidance as to how one of ordinary skill in the art would treat a human patient having a disease, disorder, or condition of the CNS by administering isolated stromal cells from a human donor. The specification does not disclose any specific disease, disorder, or condition of the central nervous system which has been subjected to the claim-designated treatment regimen, nor does the specification teach any specific methodology associated with such a treatment regimen including the number of cells to be administered for each disease, disorder, or condition, the route of administration for each disease, disorder, or condition, or the relevant cell therapy target site for the specific disease, disorder, or condition of the CNS. Nor does the specification disclose how to immunologically isolate the cells to treat a specific disease, disorder, or condition of the CNS. It should also be noted that the state of the art at the time of filing suggests that mesenchymal stem cell transplantation and *in vivo* therapeutic effectiveness have not been established such that utilizing these cells to treat diseases, disorders, or conditions is routine or predictable. For example, Prockop (Science, 276:71-74, 1997) indicates that several different strategies are being pursued for therapeutic use of MSCs, and that a phase I clinical trial demonstrated that the systemic infusion of autologous MSCs appears to be well tolerated, but also notes that "Obviously, however, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy." (see page 74, middle column). Similarly, Gerson (Nature Medicine, 5:262-264, 1999) indicates that many questions need to be addressed regarding the utilization of MSCs in therapeutic regimens including "What is the minimal proportion of donor MSCs required to affect a long-lasting therapeutic response?"; "Will transplantation of MSCs from a marrow harvest or from culture-expansion be sufficient to treat other diseases?"; "Can culture-expanded MSCs substitute for fresh marrow allografts in the correction of genetic disorders?"; "To which host tissues do infused MSCs home, proliferate, and differentiate, and using which regulatory signals?"; "Can MSCs be used effectively for gene transfer and gene delivery?"; "Is systemic infusion optimal or is infusion into a target organ required?" (see page 264, left column). With regard to treating central nervous system disorders using cell therapy,

Sanberg *et al.* (Nucleic Acids Symp. Ser., 38:139-142, 1998) disclose that "[p]erhaps the most serious problem faced in the field of cell transplantation is that of a host generated immune response to the grafted tissue. The prevailing strategy is to systemically immunosuppress the transplanted patient for extended periods of time. This, however, puts the patient at risk for other health problems" (see page 140, under "Issues of Graft Rejection"). Sanberg *et al.* also indicate that cell transplantation has also been used to treat diseases or conditions in which neurons die, such as stroke or Huntington's Disease. As these disorders involve multiple neuron populations and extensive cell death throughout the brain, it is more difficult to treat these conditions using cell transplantation (see page 141, under "Cell Transplantation in Huntington's Disease). Thus, while the teachings indicate that mesenchymal, or marrow stromal based therapies appear to be promising, the specific methodologies and clinical efficacy of such therapies with regard to treating central nervous system diseases remain to be established.

With regard to *ex vivo* gene therapy, the specification only discloses the retroviral constructs pCMV-lacZ, pCOL1-lac Z, and pCOL2-lacZ which have been used to transfect the isolated stem cells (see page 7, and Example 1). However, the specification does not teach a correlation between an effective treatment regimen and a condition, disease, or disorder of the CNS with the administration of MSCs transfected with the retroviral constructs. Similarly, the specification does not provide guidance as to which nucleic acid sequences are suitable for encoding any and all therapeutic proteins. Although claims 10 and 13 limit the therapeutic protein to a cytokine, chemokine, or neurotrophin, the specification does not provide information with regard to the source of nucleic acids which encode the cytokine, chemokine, or neurotrophin, or the identity of a cytokine, chemokine, or neurotrophin which would have therapeutic effectiveness as a result of administration of the MSCs. In addition, the specification only broadly teaches possible promoter/regulatory sequences which can be used to direct expression of the nucleic acid encoding a therapeutic protein in a transfected MSC (see page 23). Moreover, there is no teaching in the specification as to the effect of transfecting the isolated stem cells, or the effect of the expressed therapeutic protein, on the phenotypic characteristics of the isolated stem cells, i.e.,

there is no teaching in the specification that the transfected cells would maintain morphologic and phenotypic characteristics which are required in the therapeutic effectiveness of the transfected cell population. In addition, there is no teaching in the specification of a correlation between the chemokine, cytokine, or neurotrophin to be expressed and the CNS disease, disorder, or condition. Similarly, there is no teaching in the specification of a correlation between a mutated, non-functional, or under-expressed gene and a CNS disease, disorder, or condition, or whether *ex vivo* gene therapy would be effective in overcoming the disease, disorder, or condition whose etiology stems from a mutated, non-functional, or under-expressed gene. It should also be noted that gene therapies for treating central nervous system disorders are still problematic. For example, Sabate *et al.* (Clinical Neuroscience, 3:317-321, 1996) indicate that gene transfer into a give brain structure should permit local and controlled expression and release of therapeutic products. Moreover, limiting the expression of trophic factors to the therapeutic target only should avoid the severe side effects associated with intravenous or ICV administration (see page 318, left column, first full paragraph). However, Sabate *et al.* caution that there are several important issues to be resolved if gene therapy for neurological diseases is to become a reality including (1) extent of transgene expression, (2) stability of transgene expression, (3) targeting of the cells, (4) safety of the procedure, and (5) the vector large-scale production capacity (see page 318, left column, under "Recombinant Adenovirus For Gene Therapy"). Sabate *et al.* indicate that the expression of adenoviral vectors persists for several months, possibly because the CNS is partially sheltered from the immune system. However, administration of recombinant adenoviruses can lead to severe inflammatory responses (see page 320, middle column, under "Future Developments For Adenovirus", bridging right column). Based on the lack of guidance in the specification, it would require undue experimentation to determine which vector system, which promoter/regulatory sequence, which nucleic acid sequence encoding a therapeutic protein should be used to transfect isolated stromal cells which are subsequently administered to a human patient to treat a disorder, disease or condition of the CNS.

○

In view of the lack of guidance in the specification, the teachings in the prior art that there is insufficient information at this time to ascertain methods by which MSCs should be isolated, maintained, and administered, and the lack of knowledge of whether cell and gene therapy is effective, one of ordinary skill in the art would not be able to use the claim-designated methods predictably and without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite for the following reasons: it is unclear what CNS diseases, disorders, or conditions are suitable for treatment by administering isolated stromal cells; it is unclear how the isolated stromal cells are administered for each CNS disease, disorder, or condition; it is unclear how the presence of the cells effects treatment of the disease, disorder or condition; and it is unclear what clinical parameters are to be measured such that a person with a disease, disorder, or condition can be identified.

Claim 2 is rendered vague and indefinite for the following reasons: it is unclear what clinical parameters are to be measured such that a person without a disease, disorder, or condition can be identified; and it is unclear what is meant by "synergeneic" as this does not appear to be an art-recognized term, nor has the term been defined in the specification. Did Applicants intend syngeneic?

Claim 4 is rendered vague and indefinite as it is unclear which genetic diseases, tumors or traumas can be effectively treated with administration of isolated stromal cells, it is also unclear

how the genetic diseases, tumors or traumas which can be treated with the isolated stem cells are identified.

Claim 5 is rendered vague and indefinite as it is unclear what types of injuries and to what cell types are suitable for treating by administration of isolated stem cells.

Claim 6 is rendered vague and indefinite as it is unclear from the claim and the specification what types of brain tumors are amenable to treatment with isolated stem cells.

Claim 7 is rendered vague and indefinite by the phrase "remain present" as it is unclear if by remaining present the cells do not migrate from an area, do not differentiate, or are not subjected to an immune response which results in the lysis of the cells. Clarification is requested.

Claim 8 is rendered vague and indefinite as it is unclear if the *in vitro* culturing step is to expand the isolated stromal cells or to differentiate the isolated stromal cells prior to administration.

Claims 9 and 11 are rendered vague and indefinite for the following reasons: it is unclear what therapeutic protein is intended as it is unclear what type of disease, disorder, or condition is being treated; it is unclear if the nucleic acid is homologous or heterologous or from what source the nucleic acid is obtained; and it is unclear how the protein is expressed (claim 9) and secreted (claim 11), i.e., is the nucleic acid in an expression vector?

Claims 12 and 15 are rendered vague and indefinite for the following reasons: it is unclear which promoter/regulatory sequence is suitable for expression in isolated stromal cells, i.e., is the promoter/regulatory sequence from a gene which is constitutively expressed or from a gene which has tissue-restricted expression; and is the sequence a homologous or heterologous sequence?

Claim 15 is further rendered vague and indefinite as it is unclear which mutated, non-functioning or under-expressed gene is intended as it is unclear how a mutated, non-functioning, or under-expressed gene is correlated to a CNS disorder, disease, or condition.

Claim 16 is rendered vague and indefinite for the following reasons: it is unclear what is intended by "pre-differentiated", i.e., it is unclear what morphologic and phenotypic markers delineate isolated stromal cells from pre-differentiated cells from differentiated cells: it is unclear

what is required in the culture steps to allow the cells to pre-differentiate and to differentiate; it is unclear what is intended by "substantially homogeneous" as this is a relative phrase; and it is unclear which differentiated cells are required in the method, the source of the cells, or the method of obtaining the substantially homogeneous population of differentiated cells.

Claim 17 is rendered vague and indefinite as it is unclear what is intended by "pre-differentiated", i.e., it is unclear what morphologic and phenotypic markers delineate isolated stromal cells from pre-differentiated cells from differentiated cells; it is unclear how to "perform" the pre-differentiation; and it is unclear which nucleic acid is required in the introduction step and how it is introduced.

Claim 18 is rendered vague and indefinite by the phrase "immunologically isolated" as it is unclear which type of "immunologically isolated cell" is applicable in the treatment of the broadly claimed disorders, conditions, or diseases of the central nervous system, i.e., it is unclear if any "type" of immunologically isolated cell is suitable in the treatment of any disorder, condition or disease of the central nervous system.

Claim 19 is rendered vague and indefinite for the following reasons: it is unclear what is intended by "substantially homogeneous" as this is a relative phrase; and it is unclear which differentiated cells are required in the method, the source of the cells, or the method of obtaining the substantially homogeneous population of differentiated cells; and it is unclear how one determines whether the isolated stem cells acquire the phenotypic characteristics of the differentiated cell, i.e., which characteristics should be analyzed?

It is suggested that Applicants particularly point out and distinctly claim the subject matter which applicant regards as the invention as the metes and bounds of the broadly claimed diseases, disorders, conditions, nucleic acids, therapeutic proteins, promoter/regulatory sequences, tumors, injuries, immunologically isolated cells, etc., are unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eglitis *et al.* (Proc. Natl. Acad. Sci., 94:4080-4085, April, 1997), taken with Pereira *et al.* (Proc. Natl. Acad. Sci. USA, 92:4857-4861, 1995), Friedmann (TIG, 10:210-214, 1994), and Prockop (Science, 276:71-74, 1997).

Eglitis *et al.* disclose that transplantation of a population of vector-tagged donor bone marrow cells into a recipient results in subependymal concentration of the marrow-derived cells. Eglitis *et al.* indicate that the subependymal zone is an important source of neuronal and glial progenitors during development and in adults, and finding bone-marrow derived cells in this location opens the possibility that such cells receive cues guiding their differentiation once they enter the brain. Eglitis *et al.* disclose and that studies evaluating this possibility are ongoing. Eglitis *et al.* also teach that the wide distribution of GFAP-positive cells in both gray and white matter suggests that bone marrow-derived progenitors are not restricted to differentiate into a particular subclass of astroglia. That is, marrow marked cells contributed to both fibrous

astrocytes in the white matter and protoplasmic astrocytes in the gray matter (see page 4080, under "Materials and Methods", and page 4083, right column, second and third paragraphs).

Eglitis *et al.* do not disclose co-culturing isolated marrow-derived cells with differentiated cells such as astrocytes to differentiate the marrow-derived cells into differentiated cells such as astrocytes. However, Friedmann discloses that mammalian CNS contains some cellular elements that are probably derived from the bone marrow, such as microglia (see page 212, left column, first paragraph). In addition, Pereira *et al.* disclose the repopulation of tissue, including brain tissue, by adherent marrow cells intravenously administered to irradiated mice, and suggest that the adherent marrow cells serve as long-term precursor cells for these tissue (see Table 1, and pages 4859-4860, under "Discussion").

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to co-culture isolated stem cells with a population of differentiated cells, such as astrocytes to establish if the differentiated cell type alone is sufficient to provide the necessary cues to guide differentiation of the marrow-derived cells, or if the entire tissue microenvironment is required to provide the cues necessary for differentiation of the marrow-derived cells. One of ordinary skill would have been motivated to utilize such a method to determine the environmental conditions, such as growth factor requirements, cell-cell interactions between stem cells and differentiated cells, or extracellular matrix normally associated with the *in vivo* environment, that are required to direct the differentiation of marrow-derived cells into other cells types, such as astrocytes. In view of the teachings of Friedmann that marrow contains cells which can be directed to differentiate into central nervous system-associated cell types, and the disclosures of Eglitis *et al.* and Pereira *et al.* that administration of marrow-derived cells results in the differentiation of the marrow-derived cells into different lineages depending on which tissue is repopulated, and further in view of the teaching of Eglitis *et al.* that the identity of the majority of bone marrow-derived cells remains an open question (see page 4083, right column, last paragraph), one of ordinary skill in the art would have been motivated to establish cell culture conditions which allow the identification of bone marrow-derived cells, and which allow the

identification of the microenvironment required to recapitulate the *in vivo* observations of Eglitis *et al.* and Pereira *et al.* Moreover, one of ordinary skill of the art would have had a high expectation of successfully establishing the *in vitro* conditions which are permissive for directing the differentiation of marrow-derived cells into specific cell lineages, such as astrocytes, as this methodology has been previously used to direct the differentiation of the marrow-derived cells into cell types such as osteoblasts, chondrocytes, and adipose cells as disclosed by Prockop (see page 72, middle column).

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

No claims are allowed.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Brian Stanton, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-2801. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

○

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

Karen M. Hauda
Karen M. Hauda
Patent Examiner